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Figure 1

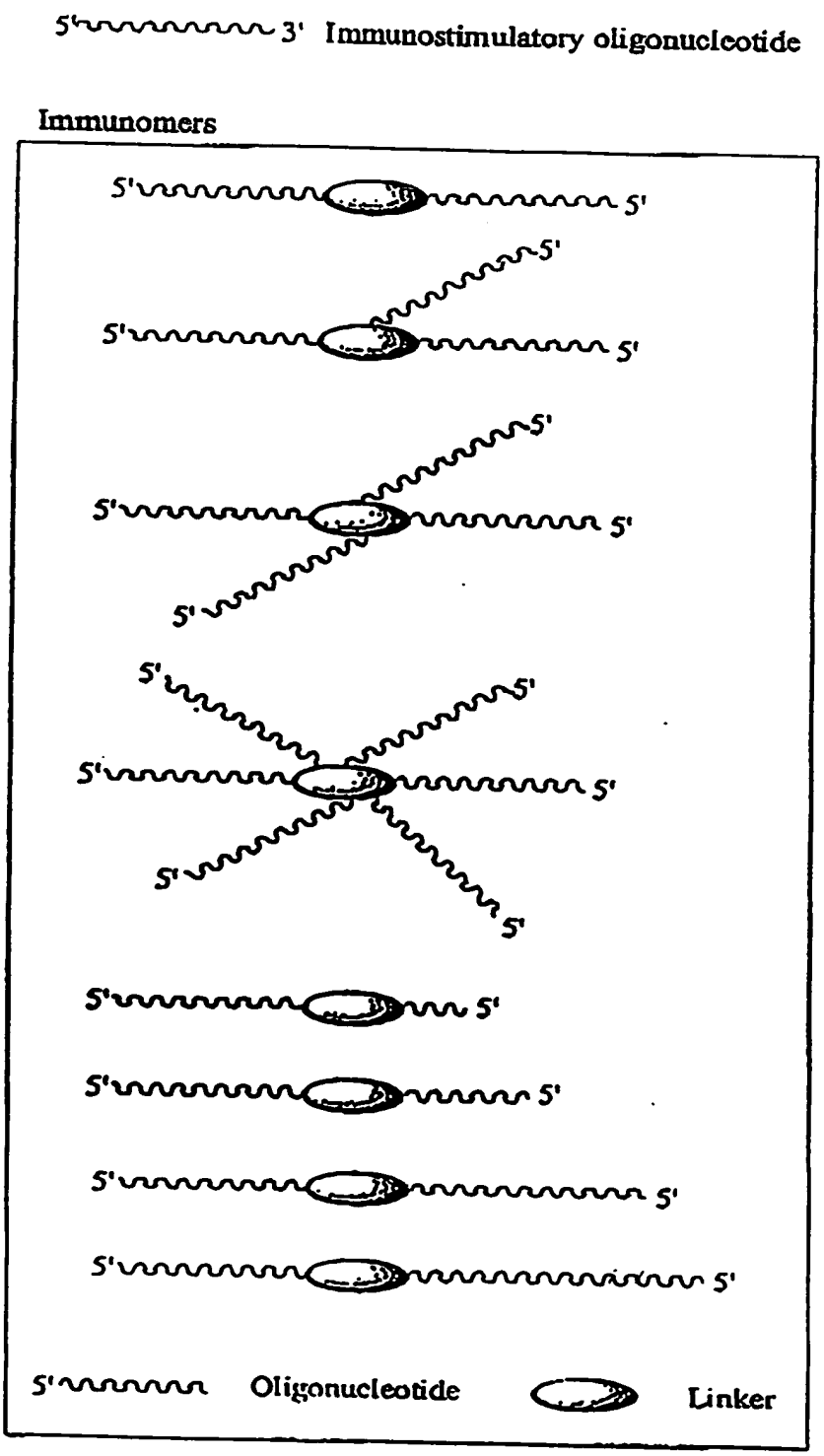

5' 3' Immunostimulatory oligonucleotide
Immunomers
Oligonucleotide
Linker

Figure 2

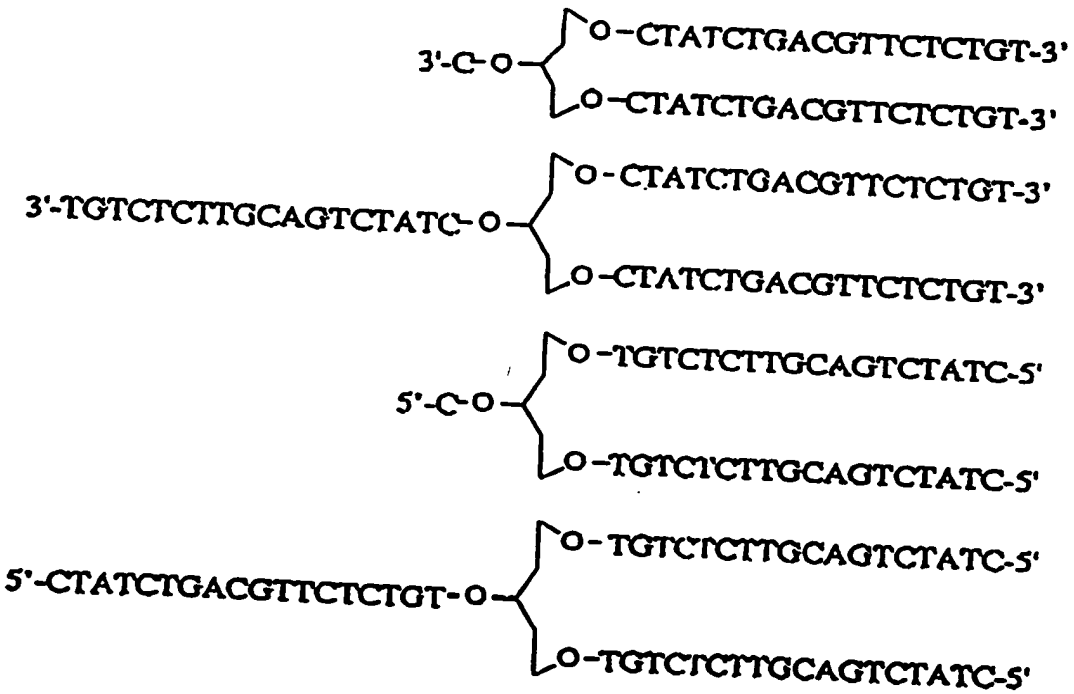

3'-C-O
O-CTATCTGACGTTCTCTGT-3'
O-CTATCTGACGTTCTCTGT-3'
3'-TGTCTCTTGCAGTCTATC-O
O-CTATCTGACGTTCTCTGT-3'
O-CTATCTGACGTTCTCTGT-3'
5'-C-O
O-TGTCTCTTGCAGTCTATC-5'
O-TGTCTCTTGCAGTCTATC-5'
5'-CTATCTGACGTTCTCTGT-O
O-TGTCTCTTGCAGTCTATC-5'
O-TGTCTCTTGCAGTCTATC-5'

Figure 3

Linkers for linear synthesis

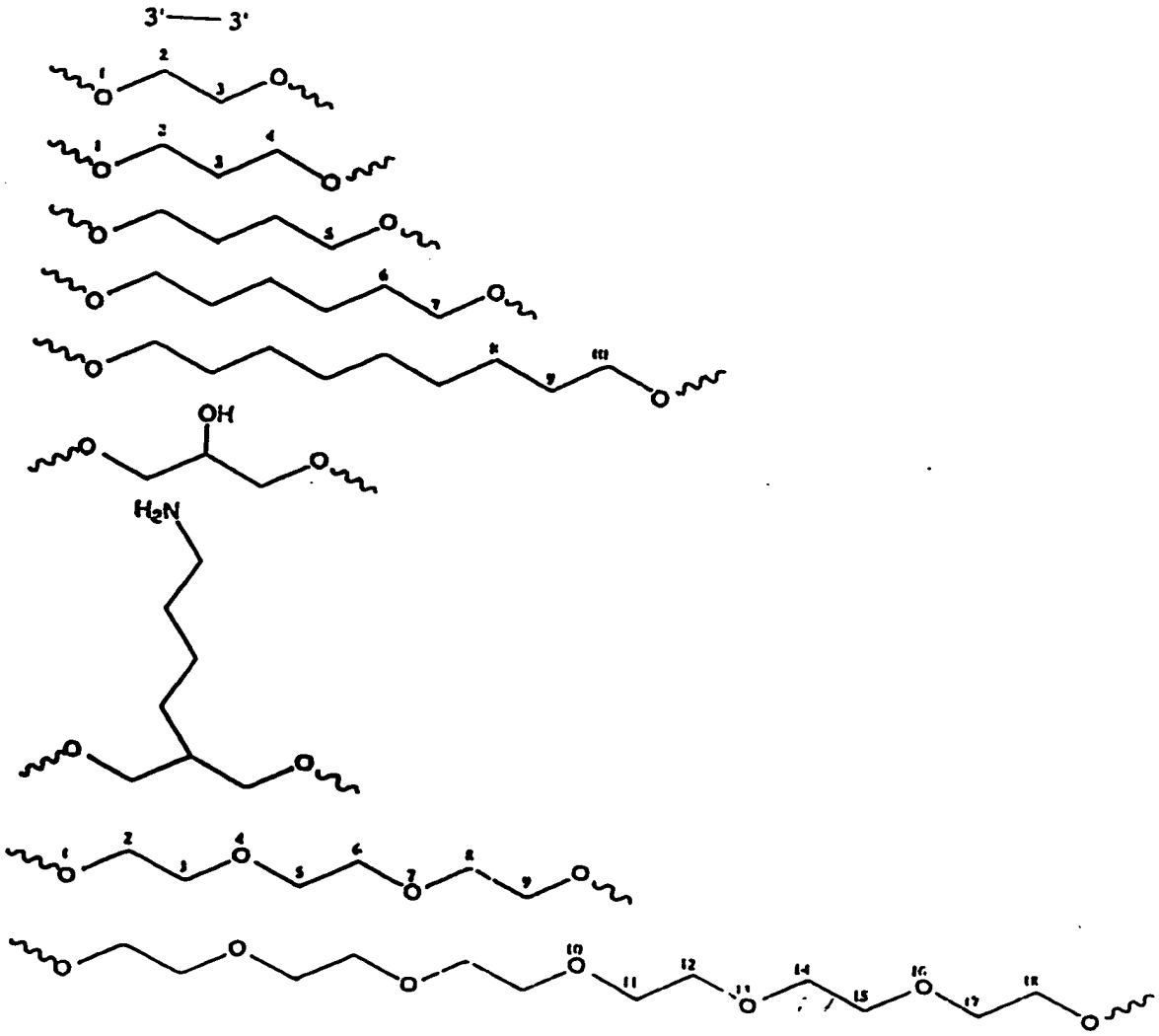
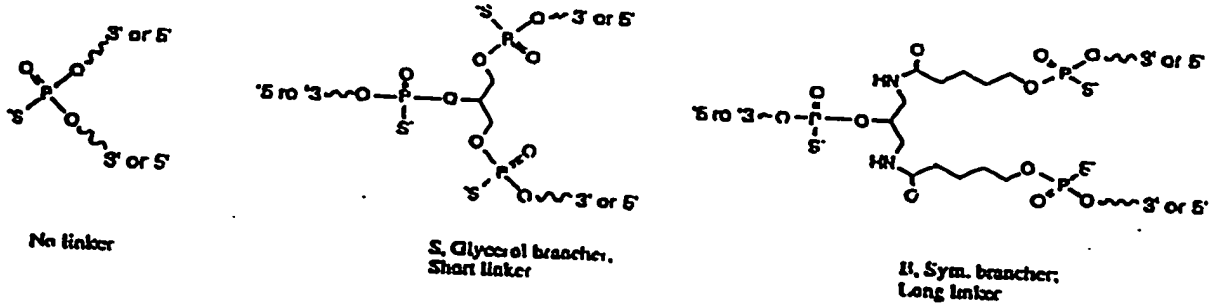


Figure 4



No linker

S. Glycerol brancher, Short linker

B. Sym. brancher; Long linker

Figure 5

Linear Synthesis of Immunomers

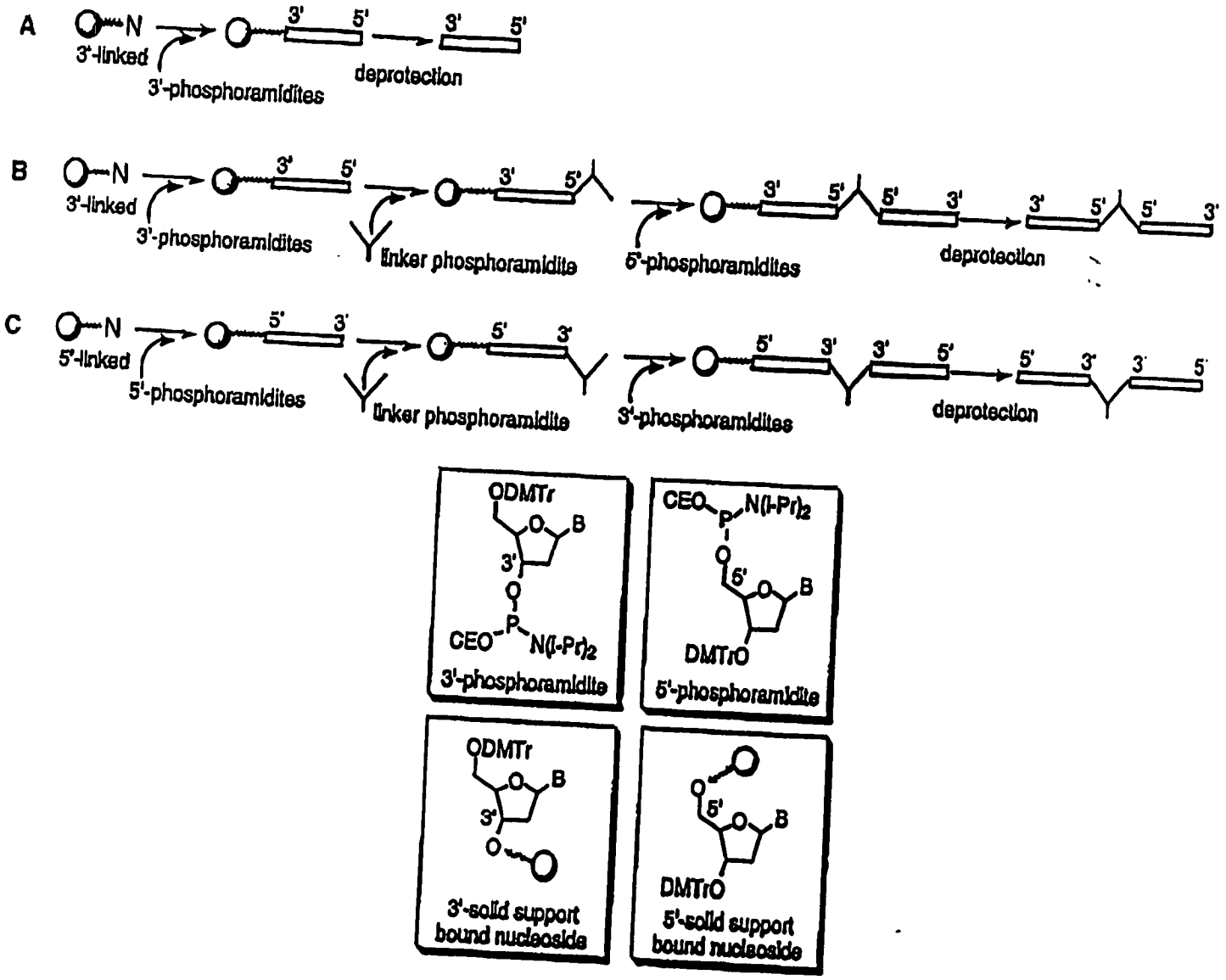


Figure 6

Parallel Synthesis of Immunomers

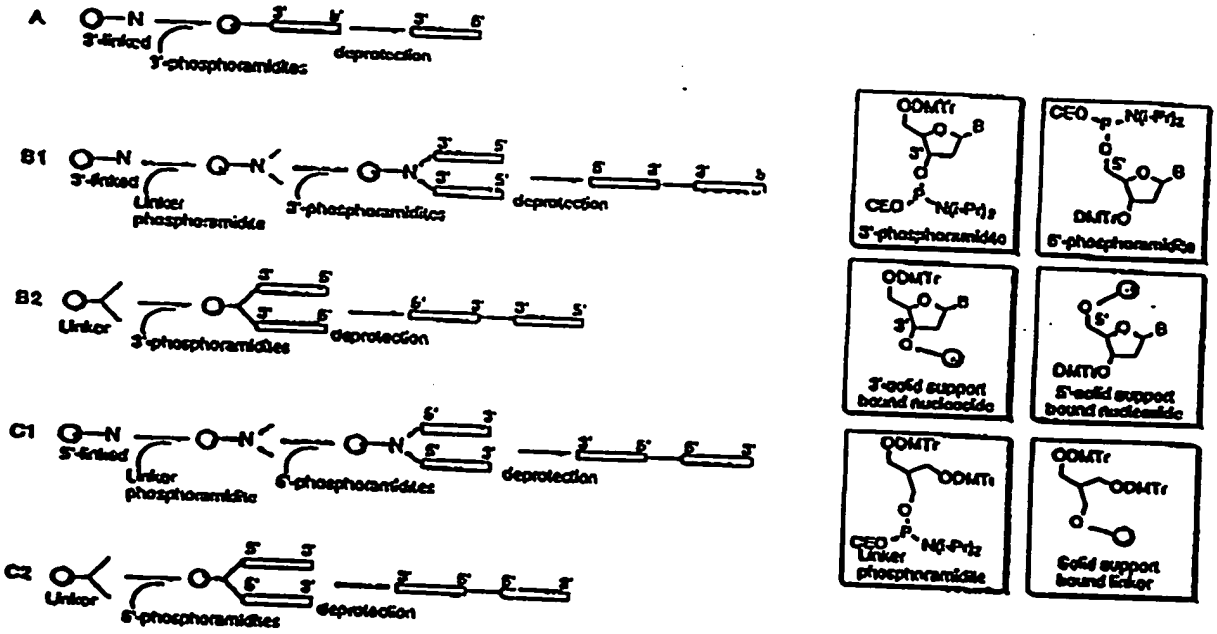


Figure 7A

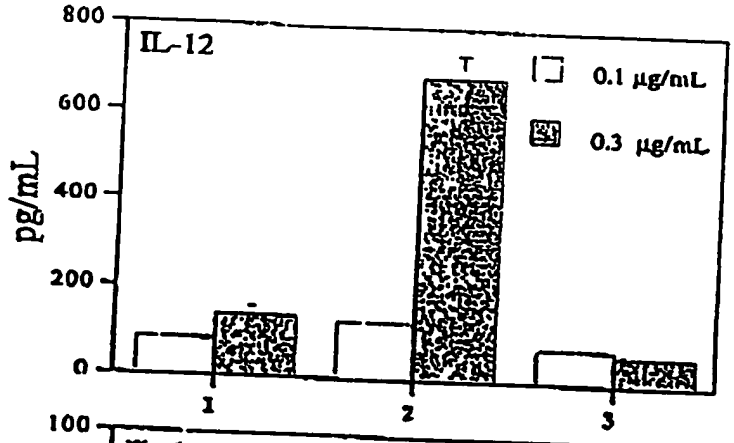


Figure 7B

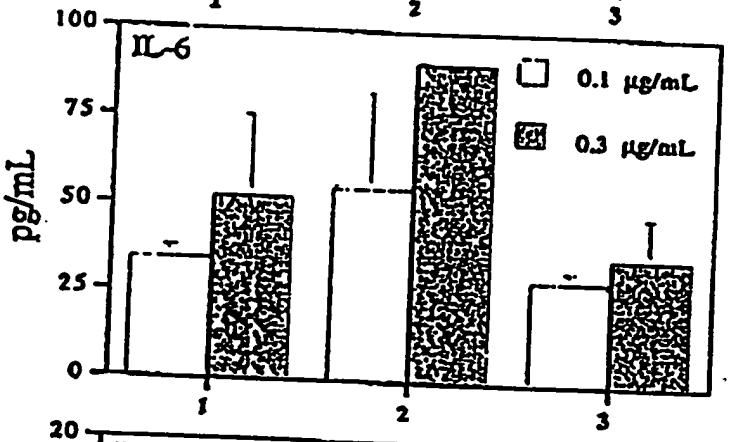


Figure 7C

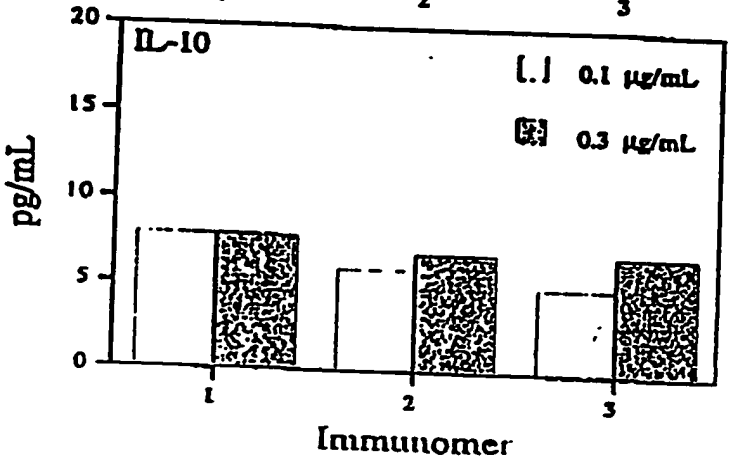


Figure 8A

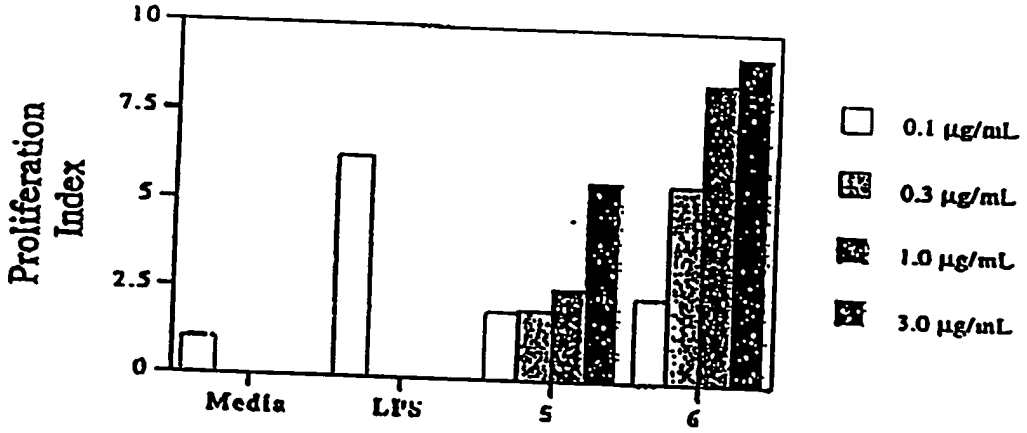


Figure 8B

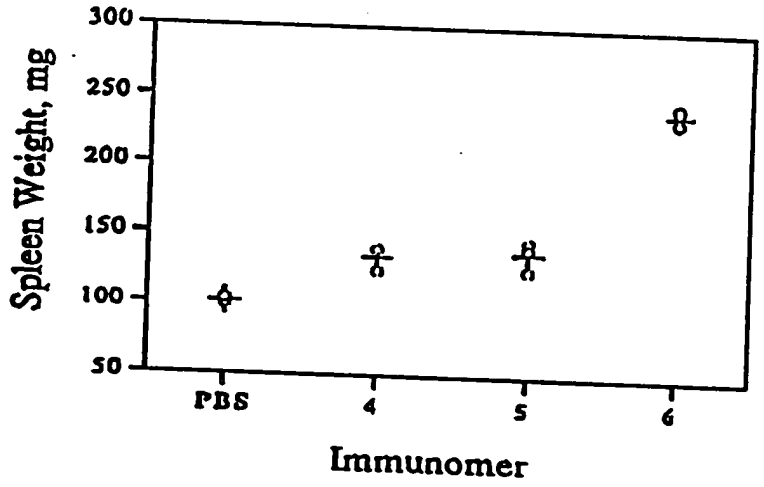


Figure 9A

Figure 9B

Figure 9C

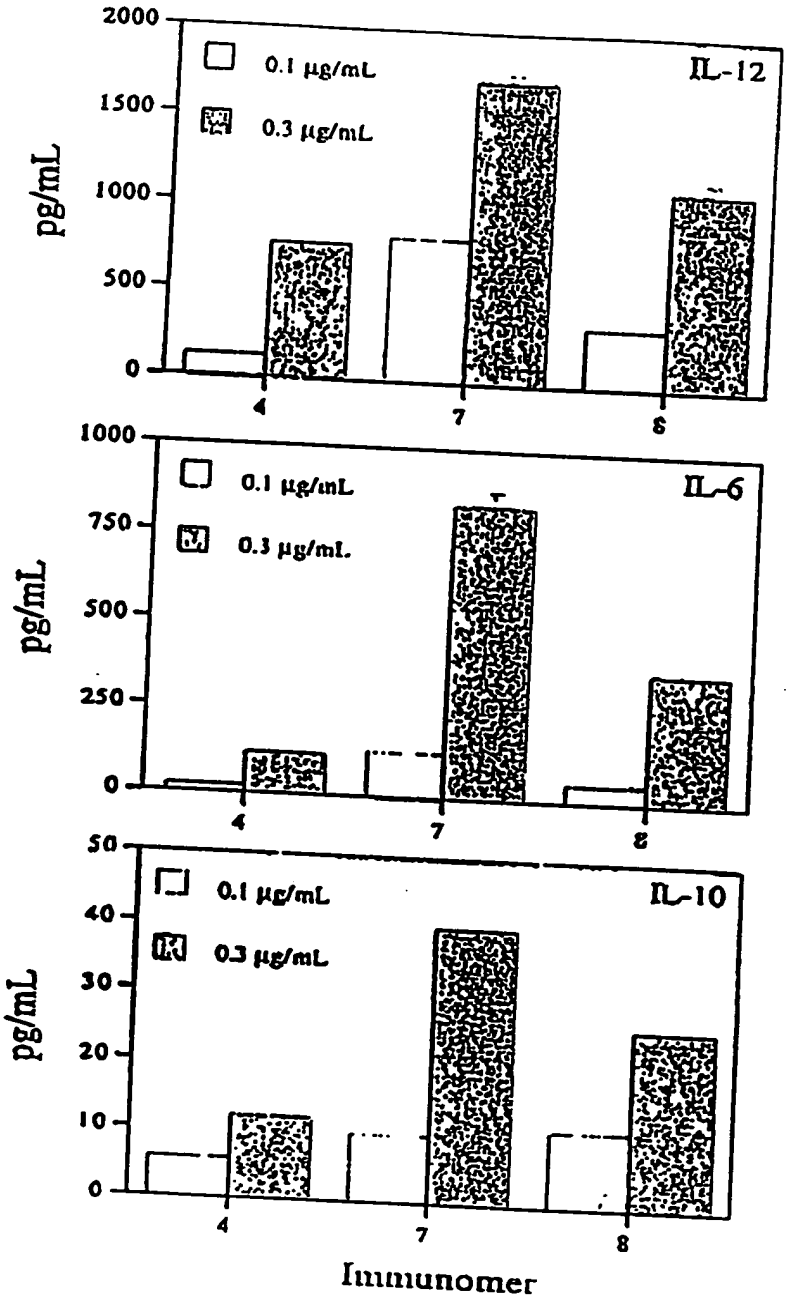


Figure 10A

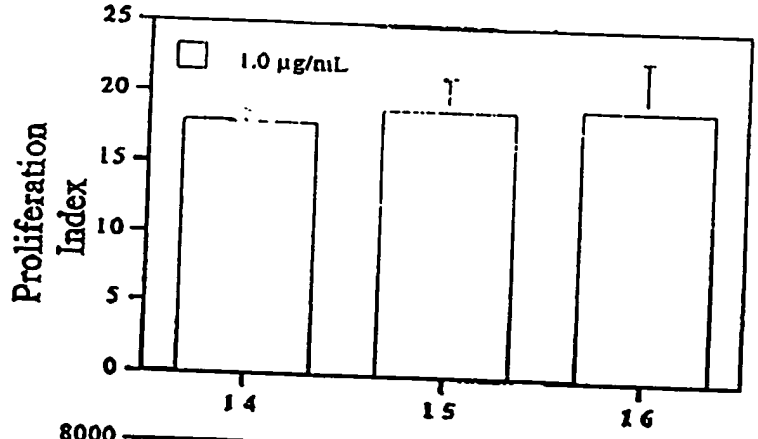


Figure 10B

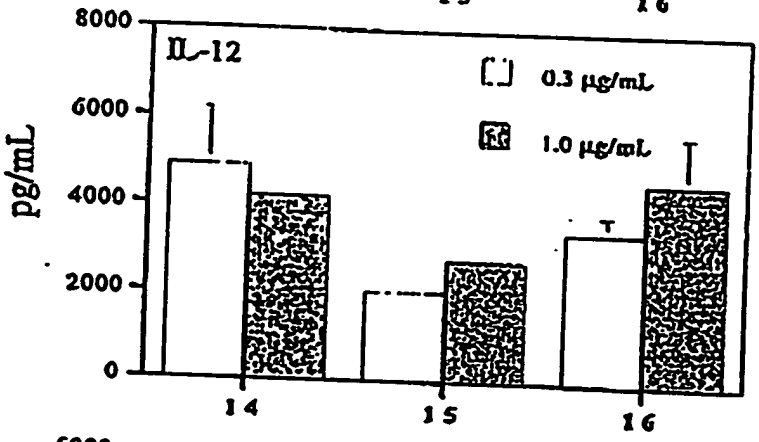


Figure 10C

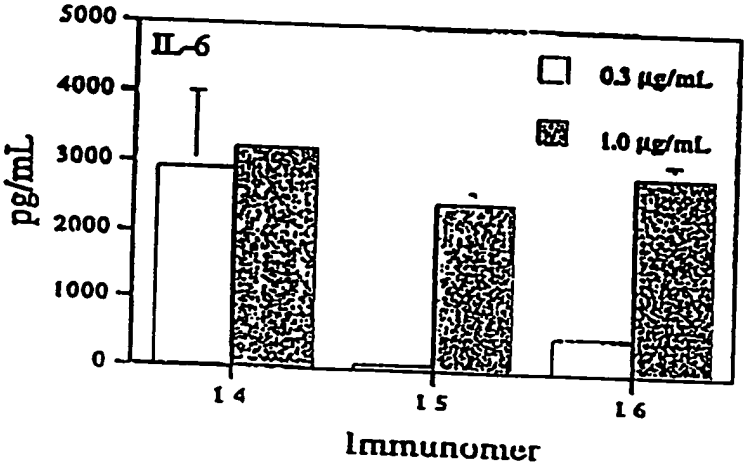


Figure 11A

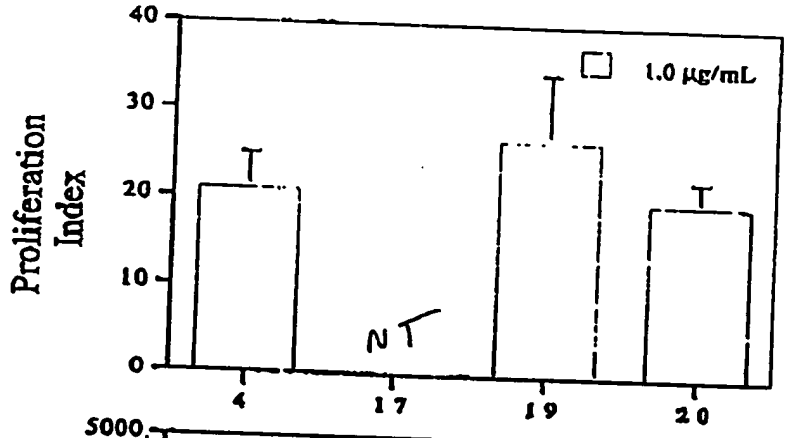


Figure 11B

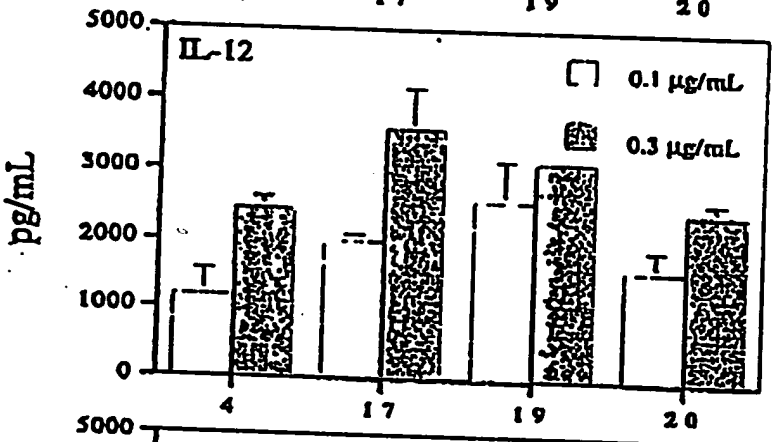


Figure 11C

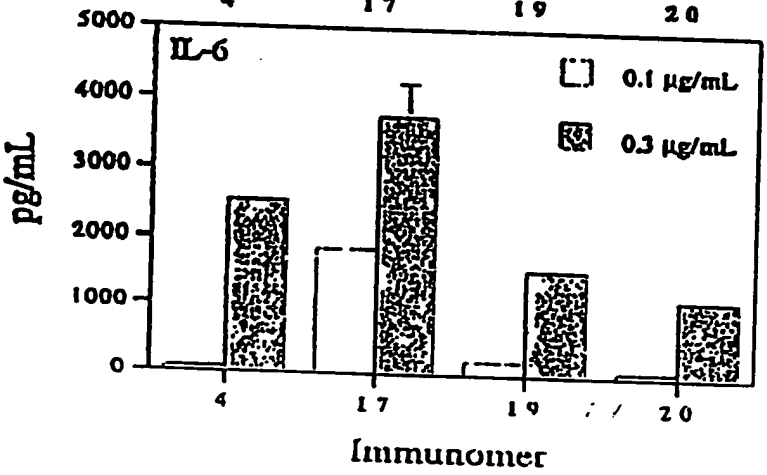


Figure 12

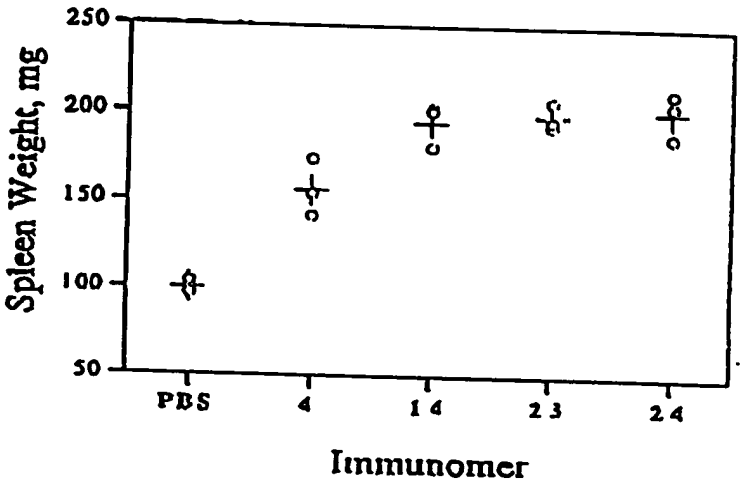
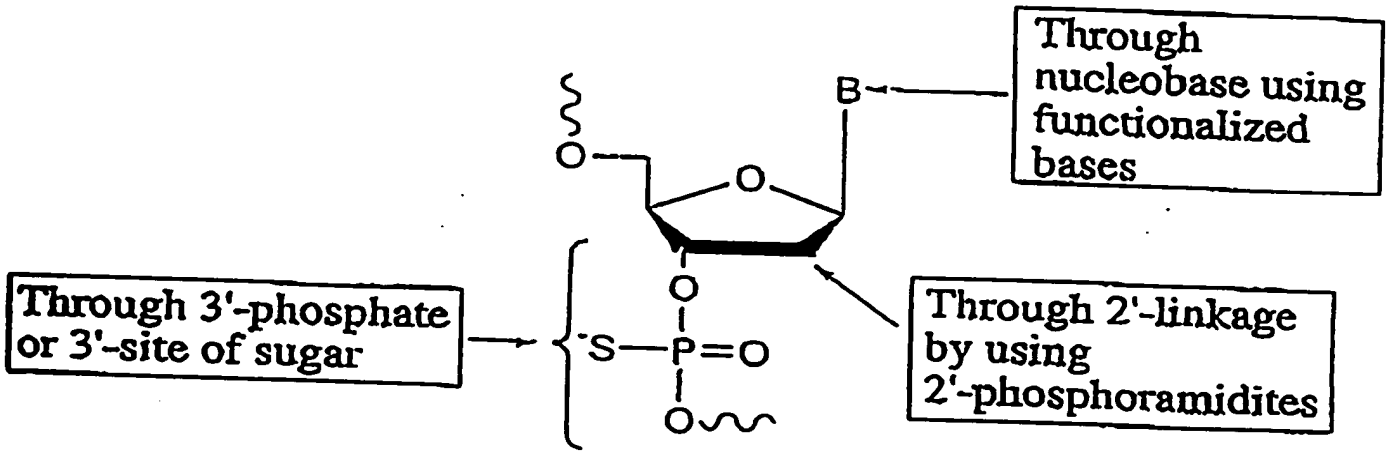
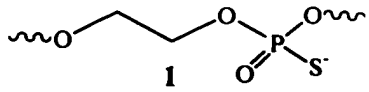


Figure 13

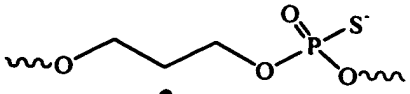
Possible sites for conjugation



A. Alkyl linkers



1



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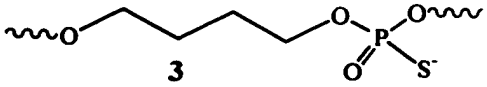

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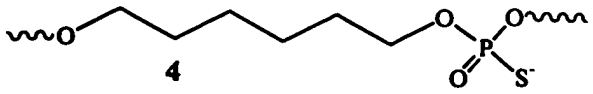

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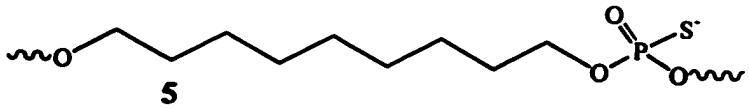
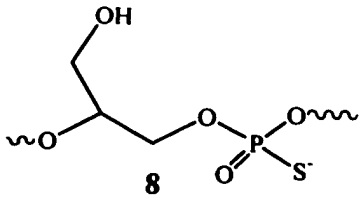


5

C. Branched alkyl linkers



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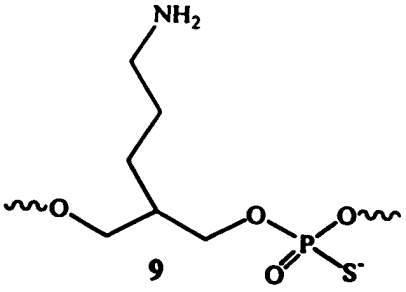
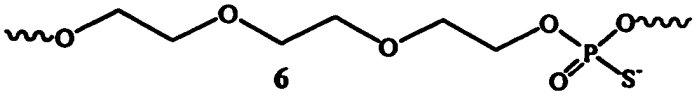


9

B. Ethylene-glycol linkers



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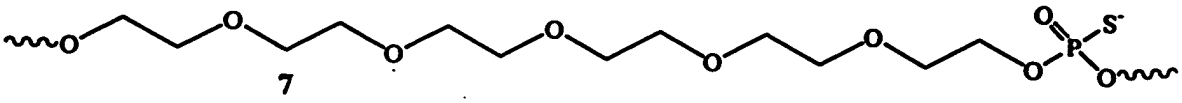


7

Figure 14

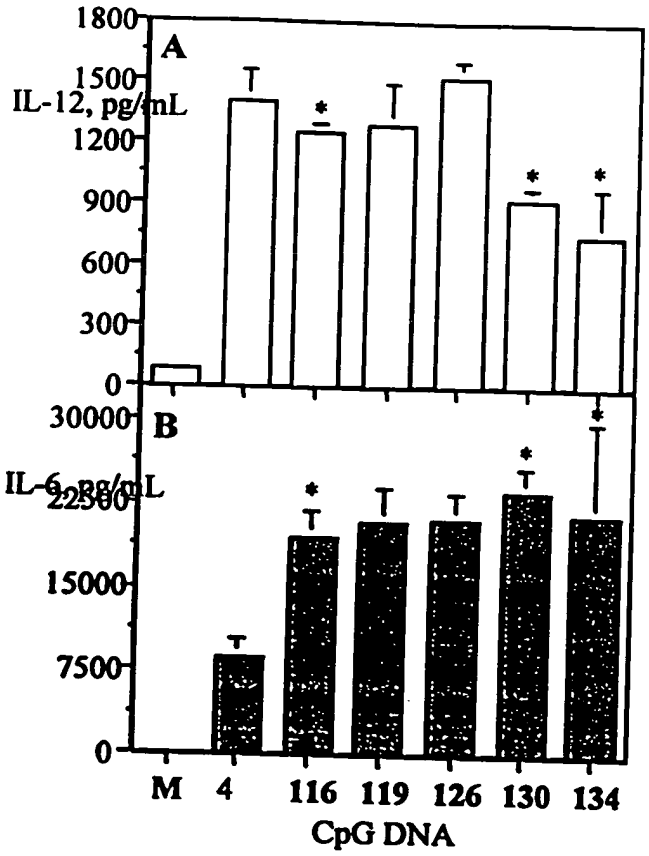

1800
1500
1200
900
600
300
0
A
IL-12, pg/mL
30000
22500
15000
7500
0
B
IL-6, pg/mL
M
4
116
119
126
130
134
CpG DNA

Figure 15

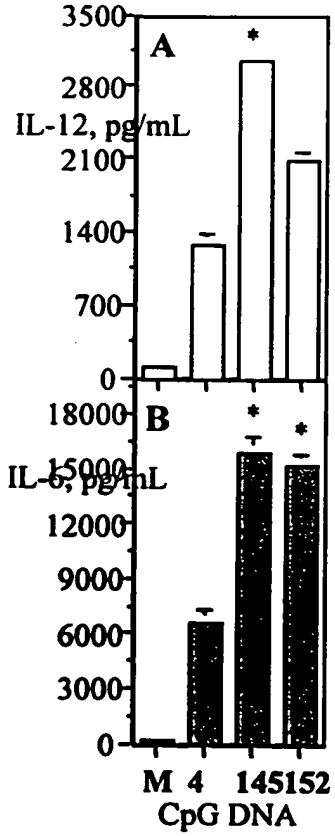

3500
A
2800
IL-12, pg/mL
2100
1400
700
0
18000
B
15000
IL-6, pg/mL
12000
9000
6000
3000
0
M 4 145152
CpG DNA

Figure 16

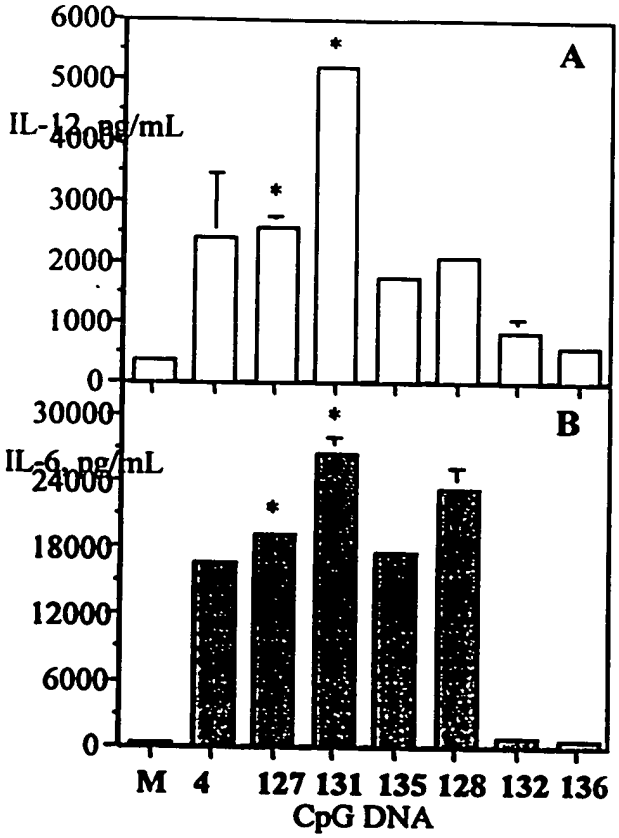

6000
5000
4000
3000
2000
1000
0
IL-12 pg/mL
A
*
*
30000
24000
18000
12000
6000
0
IL-6 pg/mL
B
*
*
M 4 127 131 135 128 132 136
CpG DNA

Figure 17

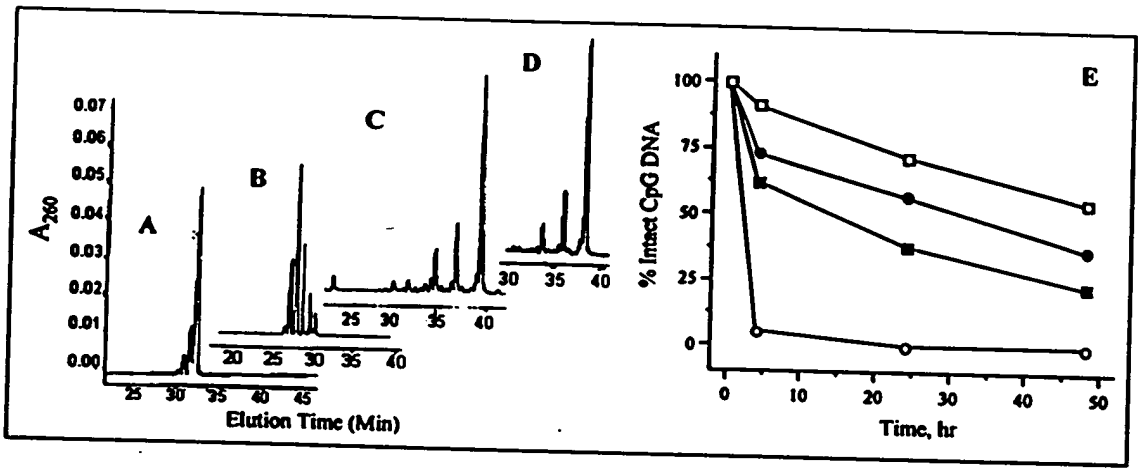

A
B
C
D
E
A_{260}
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
25 30 35 40 45
20 25 30 35 40
25 30 35 40
30 35 40
Elution Time (Min)
% Intact CpG DNA
100
75
50
25
0
0 10 20 30 40 50
Time, hr

Figure 18

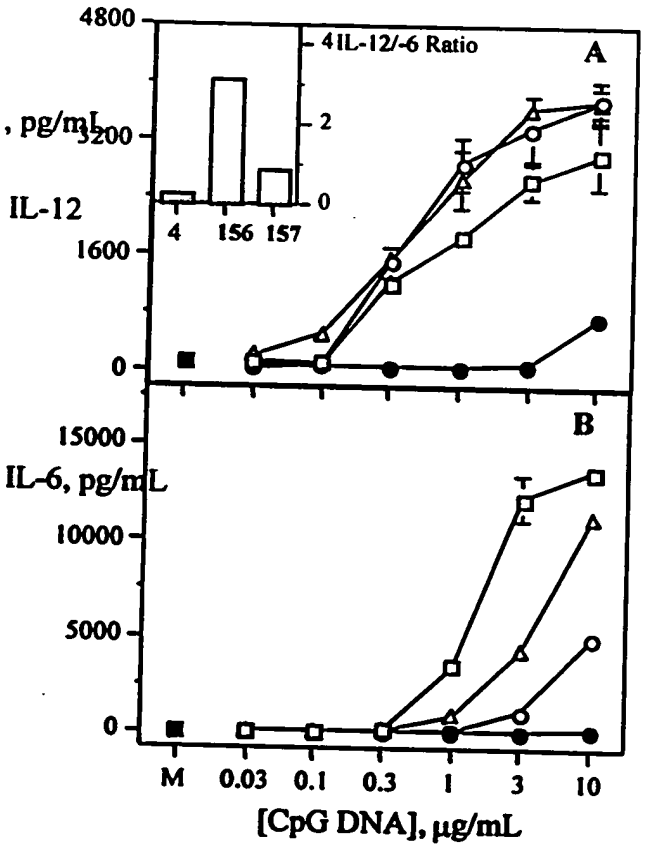

4800
3200
1600
0
, pg/mL
IL-12
4IL-12/-6 Ratio
2
0
4
156
157
A
B
15000
10000
5000
0
IL-6, pg/mL
M
0.03
0.1
0.3
1
3
10
[CpG DNA], µg/mL

Figure 19

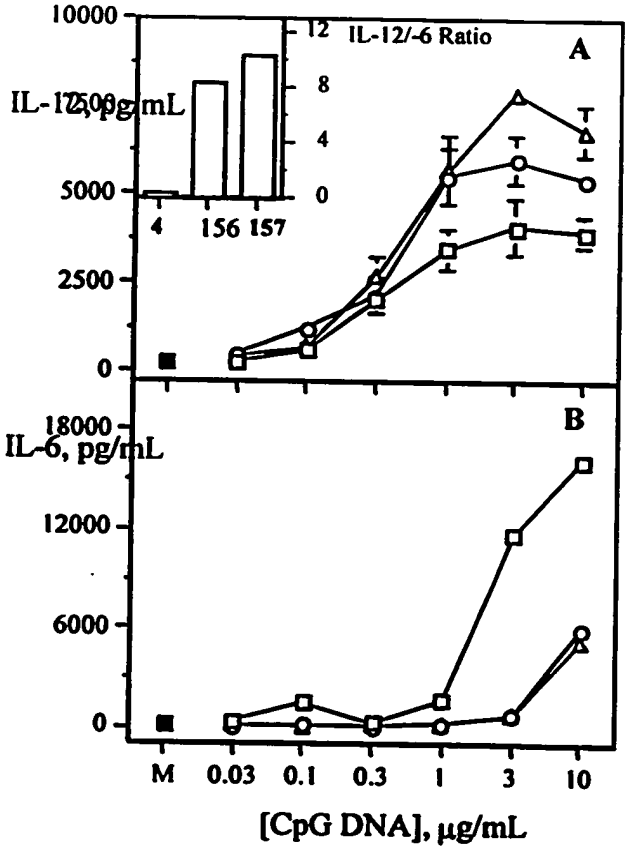

10000
5000
2500
0
IL-12, pg/mL
12
8
4
0
IL-12/-6 Ratio
A
4
156
157
18000
12000
6000
0
IL-6, pg/mL
B
M
0.03
0.1
0.3
1
3
10
[CpG DNA], μg/mL

Figure 20

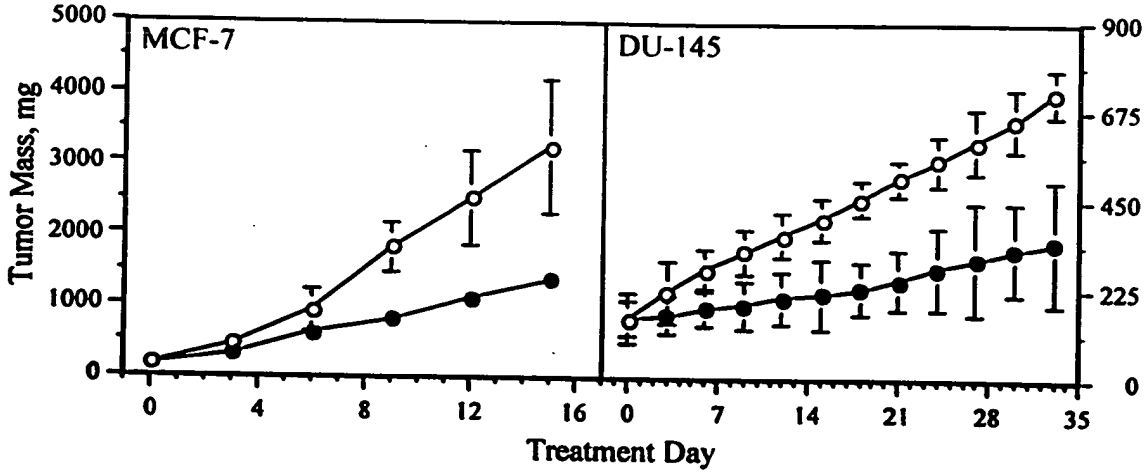
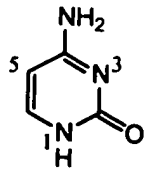
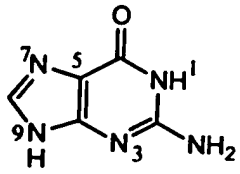

MCF-7
DU-145
Tumor Mass, mg
Treatment Day
5000
4000
3000
2000
1000
0
900
675
450
225
0
0
4
8
12
16
0
7
14
21
28
35

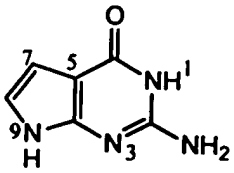
Figure 21



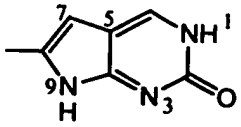
2-Oxo-4-amino pyrimidine or cytosine



2-Amino-6-oxo-purine or guanine



2-Amino-6-oxo-7-deazapurine or 7-deaza-guanine



2-Oxo-7-deaza-8-methyl-purine

FIGURE 22

1 d(5'-CTATCTGA**CG**TTCTCTGT-3')
2 d(5'-CTATCTGA**RG**TTCTCTGT-3')
3 d(5'-CTATCTGA**CR**TTCTCTGT-3')

4 d(5'-CTATCTGT**CG**TTCTCTGT-3')
5 d(5'-CTATCTGT**RG**TTCTCTGT-3')

6 d(5'-TCTGA**RG**TTCT-**L**-TCTT**GR**AGTCT-5')
7 d(5'-TCTGT**RG**TTCT-**L**-TCTT**GR**TGTCT-5')

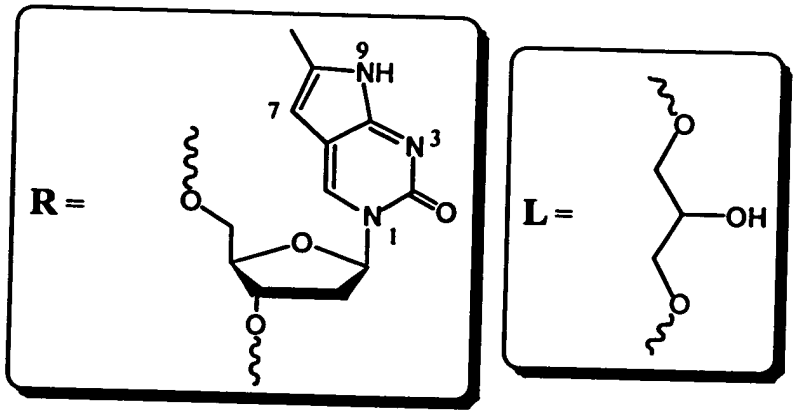
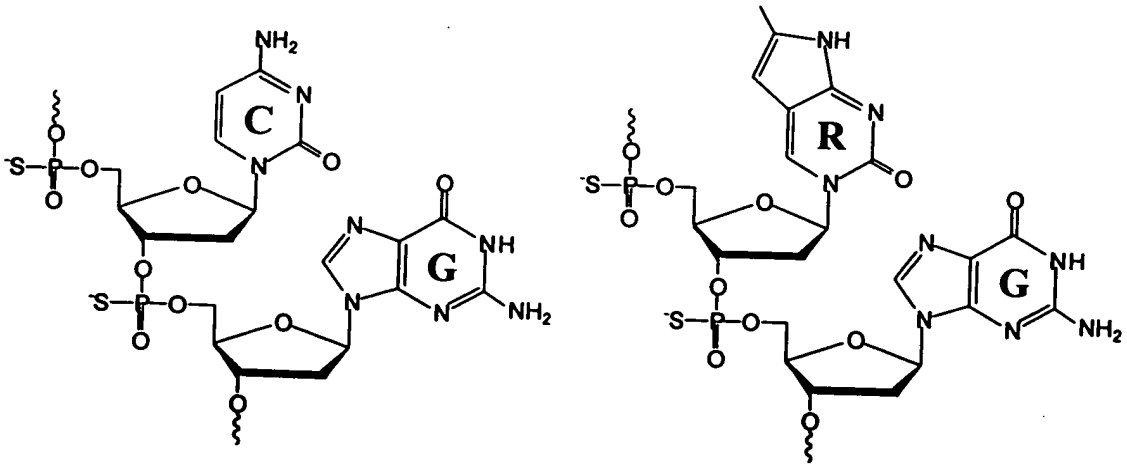


FIGURE 23

Comparison of Natural Pyrimidine-Purine Immunostimulatory Motif and Synthetic-Purine-Guanine Immunostimulatory Motif (RpG)



CpG

RpG

FIGURE 24

Immunostimulatory activity of parent oligonucleotide **1** containing CpG dinucleotide motif, oligonucleotide **2** containing RpG dinucleotide motif and control oligonucleotide **3** containing GpR dinucleotide motif in mouse spleen cell culture assays. All sequences contain mouse-specific immunostimulatory motif (GACGTT).

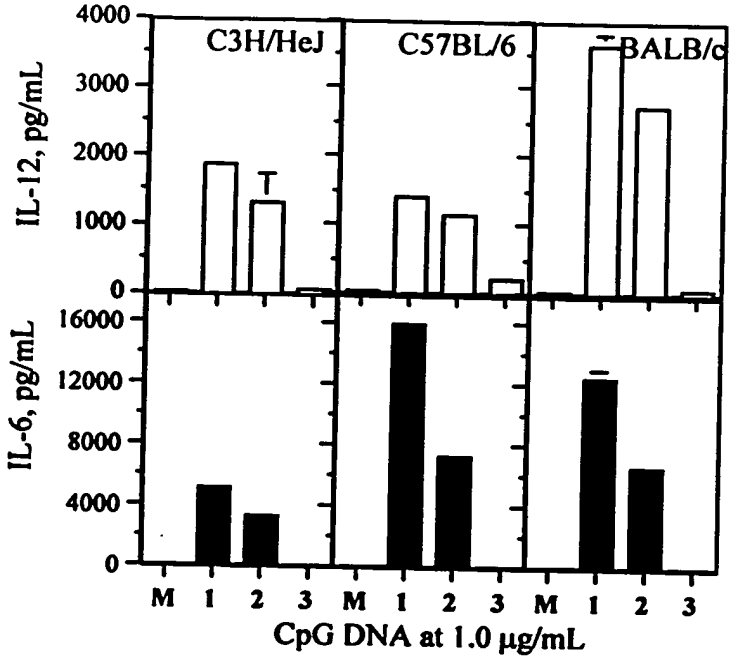


FIGURE 25

Immunostimulatory activity of parent oligonucleotide **4** containing CpG dinucleotide motif, and oligonucleotide **5** containing RpG dinucleotide motif in mouse spleen cell culture assays. All sequences contain human-specific immunostimulatory motif (GTCGTT).

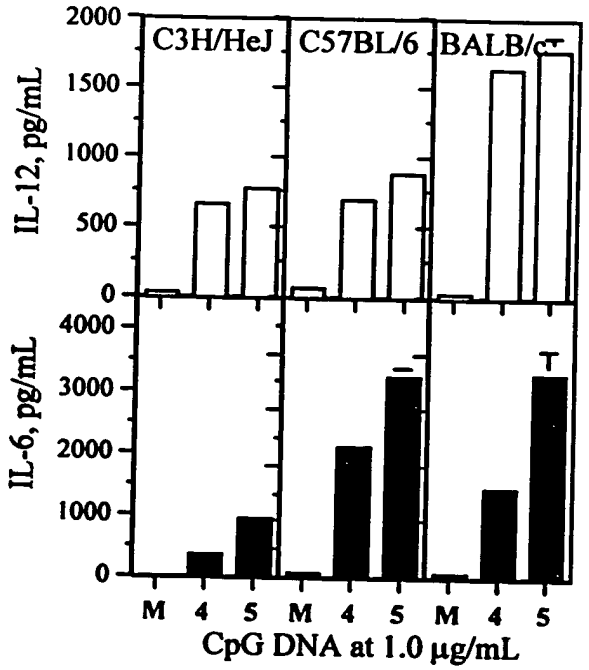


FIGURE 26

Immunostimulatory activity of parent oligonucleotides **1** and **4** containing CpG dinucleotide motif, and immunomers **6** and **7** containing RpG dinucleotide motif in mouse spleen cell culture assays. Sequences **1** and **6** contain mouse-specific immunostimulatory motif (GACGTT) and sequences **4** and **7** contain human-specific immunostimulatory motif (GTCGTT).

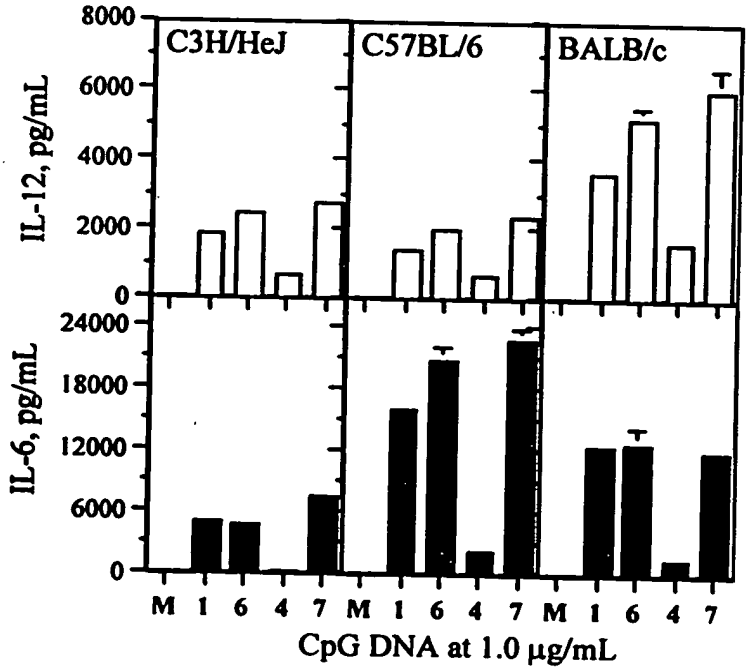


FIGURE 27

Immunostimulatory activity of parent oligonucleotides **1** and **4** containing CpG dinucleotide motif, and immunomers **6** and **7** containing RpG dinucleotide motif in J774, macrophage-like cell culture assays. Sequences **1** and **6** contain mouse-specific immunostimulatory motif (GACGTT) and sequences **4** and **7** contain human-specific immunostimulatory motif (GTCGTT).

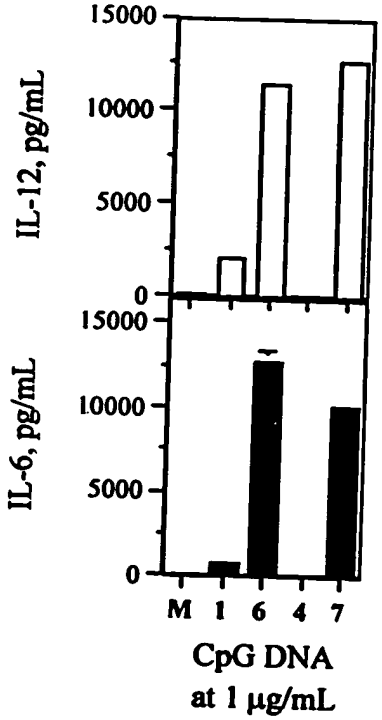


FIGURE 28

Activation of NF-κB and degradation of Iκ-Bα in J774 cells as a measure of immunostimulatory activity of parent oligonucleotides **1** - **7**.

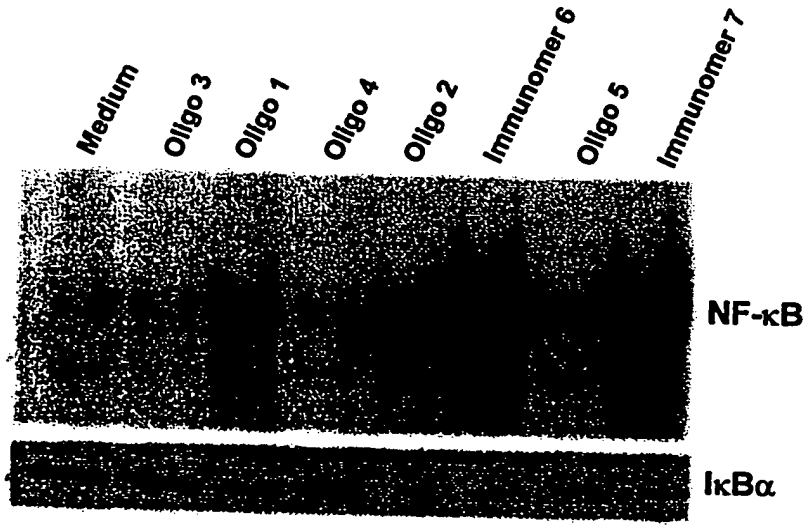


FIGURE 29

Immunostimulatory activity of immunomer 7 human PBMC cultures (one donor) at 10 μg/mL concentration.

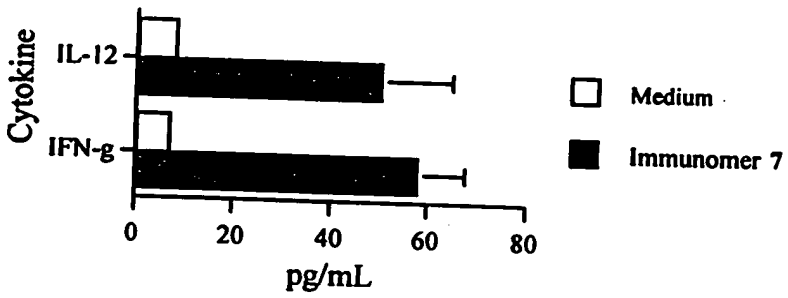


FIGURE 30